remains quantitatively in the aqueous phase and was estimated by micro Kjeldahl analysis of aliquot portions. The results are listed in the Table.

A study of the literature reveals that our results differ considerably from those obtained previously under conditions of both alkaline and acid-catalysed hydrolysis. Thus LEVENE et al.[5], who compared the rates of hydrolysis of glycine and sarcosine dipeptides *in the presence of 0.3N or 1N HCl*, found the order of reactivity to be gly-gly > sar-gly > gly-sar > sar-sar, and MORAWETZ et al.[6], in a study of *hydroxide ion-catalysed hydrolysis* of amides, found, for instance, second-order rate constants at 75.8° for propionamide $10.5 \cdot 10^{-4}$, N-methylpropionamide $1.44 \cdot 10^{-4}$, and N,N-dimethylpropionamide $2.85 \cdot 10^{-4}$ 1 mole^{-1} sec^{-1}.

Finally, under conditions most closely resembling ours with respect to pH and temperature (in the presence of 0.03*N* HCl), SCHULTZ et al.[7] found no indication of any preferential release of imino acid from proteins containing proline.

The reason for the particular behaviour of N-methyl hippuric acid is unknown. Inductive effects are unimportant since the two acids are of comparable strength (hippuric acid, pK 3.64[8], pK^{x}_{MCS} 5.74[9]; N-methyl hippuric, pK 3.50[8], pK^{x}_{MCS} 5.55[9]), and steric effects resulting in rate *acceleration* are also highly improbable. We are unable to offer a reasonable explanation, unless one postulates a rather exotic mechanism that will accommodate the special structural features and the pH dependence. The latter suggests that only undissociated acid undergoes hydrolytic cleavage. This mechanism (Figure) may be termed intramolecular nucleophilic catalysis[10], an unstable intermediate (III) being finally attacked by the water molecule.

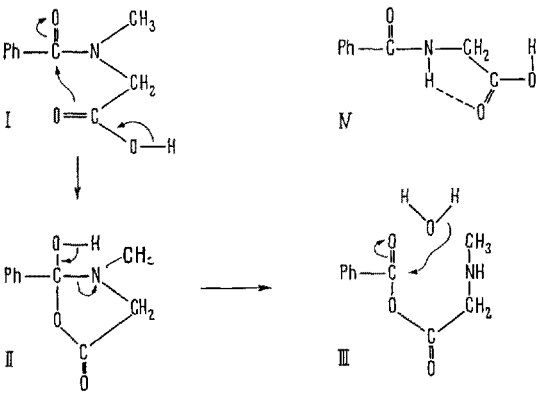
N-methyl hippuric acid, 0.025 *M* in H_2O, with added NaOH or HCl to initial pH, 9 days at 100° ± 0.2°

Exp. No.	1	2	3	4	5	6	7
pH*o*	2.45	2.21	2.57	2.77	3.06	3.50	10.68[a]
pH*t*	2.92	2.70	3.04	3.24	3.44	3.80	7.32
%h	57	63	53	52	46	34	7.9

All pH's measured at 25°. pH*o* initial, pH*t* final pH. %h = % amide hydrolysed. [a] Completely neutralized with NaOH.

By contrast, hippuric acid (IV) is thought to be stabilized by an intramolecular (or possibly intermolecular) hydrogen bond.

In conclusion, we are wondering what WITKOP[11] had in mind when he wrote: 'N-Peptides derived from proline and hydroxyproline are in a separate class because they are tertiary amides carrying no proton at the nitrogen atom. It may be possible to utilize this special feature for a preferential cleavage under proper conditions'.



Zusammenfassung. Bei 100° und pH 2,2 bis 3,5 wird die Amidbindung der N-Methylhippursäure weitgehend hydrolytisch gespalten, während Hippursäure unter denselben Bedingungen stabil ist.

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Medizinisch-chemisches Institut der Universität Bern (Switzerland), April 9, 1965.

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[6] H. MORAWETZ and P. S. OTAKI, J. Am. chem. Soc. *85*, 463 (1963).
[7] J. SCHULTZ, H. ALLISON, and M. GRICE, Biochemistry, Washington D. C. *1*, 694 (1962).
[8] Our own measurements (potentiometric titration in pure water).
[9] As determined by PD Dr. W. SIMON, E.T.H., Zürich.
[10] M. L. BENDER, Chem. Rev. *60*, 53 (1960).
[11] B. WITKOP, Adv. Protein Chem. *16*, 224 (1961).

An Apocynaceae-Alkaloid of a Novel Type

From the leaves of the New Caledonian Apocynacea *Melodinus scandens* Forst.[1] an amorphous alkaloid I could be isolated, which, when introduced directly into the ion source of the mass spectrometer, exhibits a molecular ion with the empirical formula $C_{20}H_{20}N_2O_2$. On distillation *in vacuo* or treatment with potassium *t*-butoxide in *t*-butanol I is transformed to a crystalline compound II, $C_{19}H_{20}N_2O$, m.p. 188–190°. Since all attempts to crystallize and properly purify I failed, we first turned our attention to the structure of II.

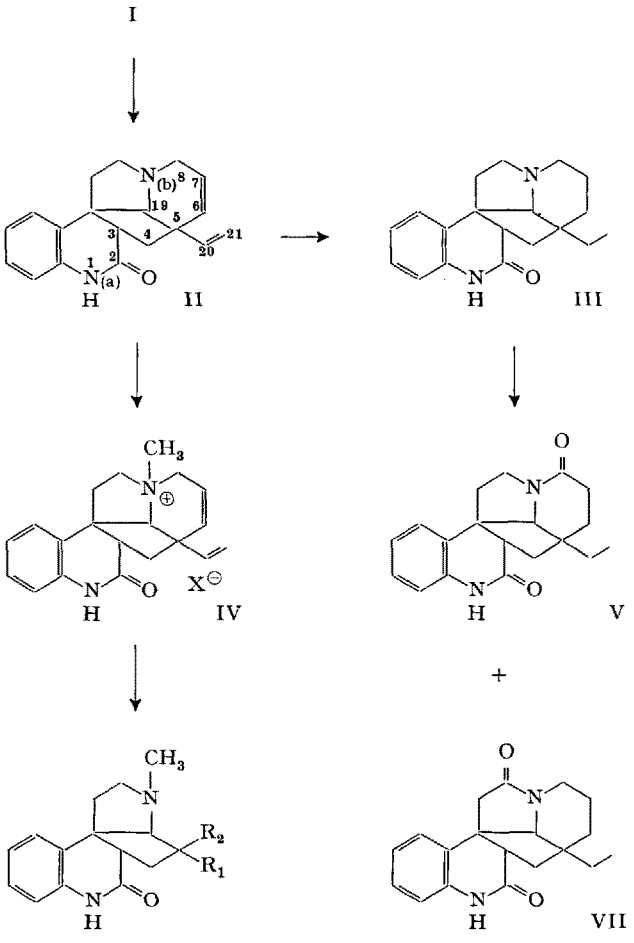
On the basis of UV, IR, NMR, and MS evidence[2] discussed below, the structures shown can be proposed for II and its derivatives III–VII.

The yet unknown structure of the natural alkaloid I will be the subject of a later publication.

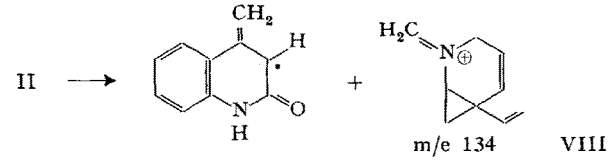
Catalytic hydrogenation of II under various conditions gives the tetrahydro compound $C_{19}H_{24}N_2O$ (III). On oxi-

[1] We are indebted to Dr. H. U. STAUFFER, University of Zürich, for the collection and identification of the plant material.
[2] MS-9 mass spectrometer (AEI, Manchester).

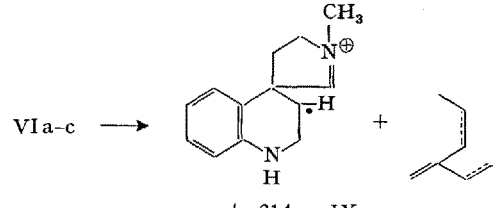
dation with potassium permanganate, III yields the dilactam V ($\nu_{C=O}$ 1680 and 1690 cm^{-1}) and the dilactam VII ($\nu_{C=O}$ 1686 and 1727 cm^{-1}, $CHCl_3$) which were purified by distillation in vacuo. Upon treatment with methyl iodide, II is transformed to its $N_{(b)}$-metho derivative IV (X = J). Hydrogenation in alkaline solution of the quaternary chloride IV (X = Cl), m.p. 278–283°, yields three different Emde-bases VIa, VIb and VIc.



VIa $R_1 = -C_2H_5$; $R_2 = -CH{=}CH{-}CH_3$
VIb $R_1 = -CH{=}CH_2$; $R_2 = -CH_2{-}CH_2{-}CH_3$
VIc $R_1 = -C_2H_5$; $R_2 = -CH_2{-}CH_2{-}CH_3$



m/e 134 VIII



m/e 214 IX

The UV- and IR-spectra of II are typical for an N-acylaniline (λ_{min} 229 mμ, lg ε 3.82; λ_{max} 253 mμ, lg ε 4.07; shoulder at 285 mμ, lg ε 3.4; ethanol. $\nu_{C=O}$ 1640, 1672 cm^{-1}; ν_{N-H} 3234 cm^{-1}; *o*-disubstituted benzene ring 754 cm^{-1}; KBr). In the 100 Mc NMR-spectrum of II[3] the following signals are observed: a singlet at about 9.5 ppm for the proton at $N_{(a)}$; a multiplet for 4 neighbouring aromatic protons at 6.7 to 7.4 ppm; a sharp singlet at 3.53 ppm for the proton at C-19; an ABC-multiplet between 4.7 and 5.7 ppm corresponding to the vinyl protons at C-20 and C-21; the AB-signals of a system

$$-CH_A{=}CH_B{-}CH_XH_Y-$$

centred at 5.75 and 6.05 ppm (protons at C-6 and C-7), the corresponding XY-part (protons at C-8) at about 3.2 ppm (proved by spin decoupling). The metho compound IV shows the XY-signal at 4.4 ppm[4]. The signals for the protons at C-3 and C-4 can be detected in the spectrum of IV. These protons give an especially clear ABX-multiplet in the spectrum of the dilactam V[3], with the X-part centred at 3.9 ppm and the AB-part centred at 2.15 ppm.

The mass spectrometric behaviour of all compounds mentioned is in agreement with the proposed structures. The most abundant fragment of II corresponds to the ion $C_9H_{12}N$, m/e 134, for which structure VIII has to be assumed. The tetrahydro compound III gives an analogous fragment $C_9H_{16}N$. The fragmentation of the three Emde-bases VIa, VIb and VIc produces intense peaks at m/e 214 ($C_{13}H_{14}N_2O$) to which structure IX can be assigned.

The hydrogen atom at C-3 in the compounds II and VIc was replaced by deuterium. Observed shifts in the mass spectra of the deuterated compounds confirm the proposed structures.

The natural alkaloid I very probably has the same skeleton as compound II. It has to be assumed that this skeleton is derived biosynthetically from an aspidospermine type precursor by oxidation at C-2 and subsequent rearrangement.

Zusammenfassung. Bei thermischer oder solvolytischer Decarbonylierung eines neuen Alkaloids aus *Melodinus scandens* Forst. entsteht eine Verbindung II, die ihrerseits in die Derivate III–VI umgewandelt werden kann. Auf Grund eingehender NMR- und MS-Untersuchungen können für die Verbindungen II–VII die angegebenen Strukturen vorgeschlagen werden. Alkaloide mit dem Skelett der Verbindung II entstehen biosynthetisch wahrscheinlich aus Alkaloiden des Aspidospermin-Typs durch Oxidation an C-2 und nachfolgende Umlagerung.

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Research Department, F. Hoffmann-La Roche & Co. AG, Basel (Switzerland), May 7, 1965.

[3] In $CDCl_3$ solution with TMS as internal standard (0 ppm).
[4] In D_2O solution with TMS as external standard (0 ppm).